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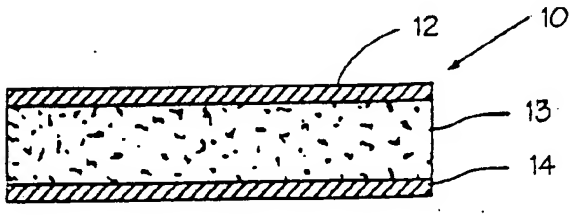

(57) Abstract

Methods for administering drugs transdermally via diffusion from a transdermal drug delivery device (10) wherein the device (10) is applied to the skin and the device (10) and skin underlying the device (10) are heated by applying an external source of heat to the device or by instigating an exothermic reaction within the device to cause the skin temperature to increase to a temperature below 45 °C and thereby cause a thermal enhancement of the flux of drug through the skin. A top layer (12) is a conductive layer that serves as a backing, for conducting heat to layer (13). Layer (12) is an adhesive polymer permeable to the drug. A release layer (14) is removed prior to use.

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THERMAL ENHANCEMENT OF TRANSDERMAL DRUG ADMINISTRATION

Description

Technical Field

This invention is in the field of transdermal drug administration. More particularly it relates to methods and devices in which the flux of the drug through the skin is increased by heating the device and the area of skin underlying the device.

Background of the Invention

Although it is well known that the flux of drug through skin is temperature-sensitive, no practical application of this principle has occurred in the transdermal drug delivery art. In this regard applicants are aware of only three references that employ heat in the transdermal administration of drugs.

U.S. 4,685,911 describes a skin patch in which the drug formulation contains a "base" that is a solid at normal temperature. It is indicated that it is desirable that the base be in a melted form while the patch is being worn. Col. 3 of the patent indicates that if the base is composed of compounds that do not melt at normal body temperature, then the device may include a heating element to heat the patch to temperatures at which such compounds melt. Accordingly, heat is used in this patent to melt a normally solid component of the device, not to enhance the flux of the drug through the skin.

U.S. 4,747,841 describes a moxibustion device. Moxibustion involves oxidizing (burning) moxa and

transporting the combustion vapors through the skin. The patented device is a skin patch that includes an in situ pyrogen that is oxidized to heat the moxa and form the combustion products. The basal surface of the device is defined by a gas-permeable fabric that acts as thermal insulation. This patent thus uses in situ-generated heat to combust moxa to form vapors that are easily absorbed through the skin. Heat is not used to increase the flux of nonvaporous materials through the skin.

U.S. 4,830,855 describes a transdermal drug delivery device that employs a side-chain crystallizable polymer diffusion matrix. The polymer undergoes a phase transition (melts) at a given temperature, below which it is impermeable to drug and above which it is substantially permeable to the drug. The device is heated either by external or internal means to cause the matrix to melt and become permeable to the drug. Accordingly, heat in this device is used to melt a component of the device so that the component becomes permeable. Heat is not used to enhance the diffusion of the drug through the skin.

The present invention is particularly useful for administering drug types that are most efficacious when administered in an initial pulse or burst that affords a rapid onset of therapeutically effective blood levels. Such types of drugs are analgesics, sedatives, anti-emetics, appetite suppressants, anti-anxiety drugs, and anti-depressants. Applicants are aware of two prior transdermal device designs that have been proposed for providing an administration regime that is initiated by a pulse. Neither of them involves heating the device and/or the area of skin underlying the device.

The first of these designs is described in U.S. Patent No. 4,060,084. It involves use of a drug reservoir layer in which the bulk of the drug is

contained, an underlying rate-controlling membrane that controls the release rate of the drug from the reservoir, and a basal adhesive layer that is loaded with drug. When this type of device is placed on the skin, the drug in the adhesive migrates rapidly into the skin providing a "burst." The burst is followed by the controlled delivery of drug from the reservoir via the rate-controlling membrane. The second design is described in U.S. Patent No. 4,698,062. It uses a first reservoir which contains a sufficient amount of the drug to provide a baseline flux over the entire administration period and a second reservoir which contains a permeation enhancer in an amount that is sufficient to provide enhancement only during the beginning of the administration period. With this design, the magnitude and duration of the period of enhanced drug flux is apparently dependent only upon the amount of enhancer contained in the second reservoir and its effect on skin flux. The patent indicates that this pattern of drug release may be achieved with various enhancers including ethanol, n-decylmethylsulfoxide, dimethyl lauramide, and polyethylene glycol monolaurate.

Disclosure of the Invention

One aspect of the invention is a method for administering a thermally stable drug transdermally to a human patient via diffusion of the drug from a transdermal drug delivery device affixed to an area of skin of the patient in which the flux of drug through said area is enhanced thermally for a predetermined time period comprising:

(a) applying the device to said area, said device comprising a reservoir of the drug in diffusional communication with said area and having no solid

component that melts below 45°C and wherein the drug is thermally stable below 45°C; and

(b) heating the device and said area of skin for said predetermined time period to a temperature substantially above the normal temperature of the skin with the proviso that said area is not heated above 45°C, whereby the flux of the drug through said area is increased.

Another aspect of the invention is a device for administering a thermally stable drug transdermally through an area of unbroken human skin comprising in combination:

(a) a reservoir of the drug in diffusional communication with the area of skin, said drug being capable of permeating through said area of skin at normal skin temperature at a first flux and being thermally stable at temperatures below 45°C, said device having no solid component that melts below 45°C; and

(b) means for heating the device and said area of skin to a temperature substantially above normal skin temperature, with the proviso that said area of skin is not heated above 45°C, whereby the flux of the drug through said area of skin when the device and skin are so heated is substantially greater than said first flux.

Brief Description of the Drawings

Figure 1 is an elevated cross-section (not to scale) of one embodiment of the invention.

Figure 2 is an elevated cross-section (not to scale) of a second embodiment of the invention.

Figure 3 is an elevated cross-section (not to scale) of a third embodiment of the invention.

Figure 4 is a graph of the results of the skin flux tests described in the example.

Modes for Carrying Out the Invention

As used herein the term "drug" intends a biologically active compound or mixture of compounds that has a therapeutic, prophylactic, or other beneficial effect on the wearer of the device. It is particularly useful for administering drugs where a rapid onset of efficacy is desired. Examples of such drugs are: sedatives, hypnotics and antianxiety agents such as diazepam, midazolam, lorzipam and alprazolam; barbituates such as pentobarbital and secobarbital; antihistamines such as hydroxyzine, diphenhydramine, promethazine and propiomazine; buterophenones such as droperidol; opioids such as morphine, meperidine, fentanyl, sufentanyl, and alfentanyl; antiemetics such as droperidol, hydroxyzine, benzquinamine, scopolamine, and cyclizine; anticholinergic drugs such as atropine, scopolamine, and glycopyrrolate; and alpha 2 agonists such as clonidine and dexmedetomidine.

As used herein the term "flux" intends the rate of transfer of drug across skin as measured by the in vitro human cadaver skin tests described in Medical Device and Diagnostic Industry (1985) 8:35-42, with the proviso that the temperature at which the test is carried out may be altered per the invention. The units of flux are preferably expressed as $\mu g/cm^2/hr$.

As used herein the term "thermally stable" intends a drug that has no substantial chemical reactivity with the other components of the device or the surrounding environment (e.g., air) and does not degrade or otherwise alter its chemical or physical nature at the temperatures to which the device is heated per the invention.

As used herein the term "normal skin temperature" intends that range of temperatures in which

healthy living human skin exists under normal living conditions. This range is normally 35 to 37°C.

As used herein the term "predetermined time period" will usually denote a period of time in the range of 0.5 to 8 hrs, more usually 1 to 4 hrs. Relative to the entire period over which drug is administered transdermally to the patient, the "predetermined time period" during which the device and skin are heated may come at the beginning, at the end, or at an intermediate time of the entire period. Further, the heating may be repeated during the entire period, meaning that there can be a multiplicity of "predetermined time periods" during the entire administration period. The entire administration period will usually last 1 to 7 days, more usually 1 to 3 days.

The devices of this invention will normally be either the conventional "matrix" type or "reservoir or container" type. In the matrix type the drug is dispersed in a solid or semisolid matrix or carrier. The devices of Figures 1 and 2 depict two such matrix-type devices, generally designated 10 and 11, respectively. Device 10 is a three-layer laminated composite. The top layer 12 is a conductive layer (e.g., metal foil) that serves as a backing and a means for conducting heat from an external source (not shown) to the underlying matrix layer 13. Matrix layer 12 is composed of a dispersion of drug in an adhesive polymer carrier that is permeable to the drug. Permeation enhancers may also be dispersed in the carrier if desired. The amount of drug in the matrix will be sufficient to provide the drug at the desired fluxes over the intended administration period. This will vary from drug to drug. Examples of adhesive polymer carriers useful for formulating the matrix are polysiloxanes, polyacrylates, plasticized ethylene-vinyl acetate copolymers (PEBAX copolymers), polyurethanes, and

rubbery polymers such as polyisobutene. The bottom layer is a conventional strippable release liner layer 14 which is removed prior to use to expose the basal surface of layer 13. In operation, the release liner is stripped from the bottom of the composite to expose the underside of the drug-containing adhesive layer 13. The bilayer device is then placed on the skin with the underside of layer 13 contacting and adhered to the skin. This places the device in diffusional communication with the skin. In other words, the matrix is in direct contact with the skin so that the drug that is dissolved in the carrier will migrate from the carrier to the skin due to the drug concentration gradient between the carrier and the skin. It will be appreciated that the matrix need not be in direct contact with the skin and that other drug-permeable layers may be interposed between the matrix and the skin as long as a diffusional pathway between the matrix and the skin is maintained.

The area of unbroken skin that is in diffusional contact with the matrix is that area which is heated per the invention. This area will normally be 10 to 100 cm^2, more usually 20 to 60 cm^2 in size.

After device 10 is placed on the skin, a heat source (direct conduction, radiation, etc.) is placed in contact with conductive layer 12. Heat is conducted from layer 12 through the matrix 13 to the underlying skin. The extent of heat transfer is controlled (e.g., by the temperature of the source and/or the duration of contact) so as to avoid heating the underlying skin above 45°C. In this regard, prolonged heating of the skin at 45°C or above may cause pain or damage (scalding or burning) to the skin. It will be appreciated that conductive, inductive, or radiant external heat sources may be used to heat the device and underlying skin. The extent of the heating will be sufficient to raise the temperature

of the underlying skin above the normal skin temperature, typically to between about 40°C and 45°C. Depending upon the duration of heating and the efficiency of heat transfer between the device and underlying skin, the temperature of the device may be approximately the same as the skin or greater than the heated skin temperature. Typically it will be the same as or within about 10°C hotter than the skin. The increase in temperature results in an increase in flux (usually between about 10% and 1000% increase)--which is believed to correspond primarily to an increase in the solubility of the drug in the carrier and the underlying skin and an increase in molecular movement within the device and the underlying skin. It is noted in this regard that no normally solid component of device 10 (or of the devices of Figures 2 and 3) melts at the temperatures to which the device is heated per this invention. Accordingly, the increase in flux achieved by the present invention is not due to melting of one or more components of the device.

Figure 2 illustrates an alternative embodiment of a matrix-type device. This device, generally designated 11, includes an internal heat-generating means. Like device 10, device 11 includes a heat-conducting layer 15, a drug-containing adhesive polymer matrix 16, and a removable release liner layer 17. Overlying this assembly are two reservoirs 18 and 19 that are separated by a pressure-rupturable wall member 20. The reservoirs are backed by a backing layer 21 that is sealed to the conductive layer about the periphery of the reservoirs. The respective reservoirs contain first and second chemical species 22 and 23 which, when combined, react exothermally (without explosion). In this regard the heat will typically be generated via heat of combustion (oxidation) or heat of solution. Controlled oxidations such as those used in commercially available

handwarmers (e.g., reaction between iron filings, salt and water) will normally be employed. Similarly, salts or other compounds which have a substantial positive (i.e., generate heat) heat of solution when dissolved in water may be used. See Handbook of Chemistry and Physics, Chemical Rubber Publishing Co. (1960) pp. 1807-1831 and the CRC Handbook of Chemistry of Physics, CRC Press, Inc. (1985) pg. D-122. The conductive layer 15 is, of course, impermeable to chemical species 22 and the reaction products of species 22 and 23. In operation, release liner 17 is removed and the device is placed on the skin with matrix 16 in diffusional communication therewith. Pressure is then applied to backing 21 and wall 20 to cause wall 20 to rupture and allow the two chemical species to mix and react. The resulting heat generated by the reaction is transferred via conducting layer 15 to the matrix 16 and thence to the underlying skin. Accordingly, the matrix and underlying skin are heated and the flux of the drug through the skin is increased as in the operation of the device of Figure 1. In alternative designs, exothermic reactions may be instigated by external means (e.g., application of moisture or radiation to a chemical or chemicals) rather than by mixing two chemical species.

Figure 3 illustrates a reservoir-type device, generally designated 25. The device is composed of a conductive overlay 26, a backing layer 27, a drug-containing reservoir 28 wherein the drug is a liquid or is in solution, a drug-permeable membrane 29, a peripheral adhesive 30, and a release layer 31. The heat-conducting overlay 26 serves the same function as layer 12 of the device of Figure 1, namely, to conduct heat from an external source to the underlying structure. Overlay 26 will be made of materials such as metal foil or polymer containing metal powder. Backing layer 27

serves as a partial means for defining and containing reservoir 28. The underlying membrane 29 serves as the other member which defines the basal wall of the reservoir and serves as a basal confinement means. Layer 27 will normally be made of drug-impermeable materials such as polyesters or polypropylenes. The drug reservoir will comprise the drug and, if the drug is not itself liquid, a liquid carrier in which the drug is dissolved. Membrane 29 is permeable to drug and defines a diffusional pathway for drug to migrate from the reservoir to the skin. It is heat sealed at 32 to the backing 27 about the periphery of the reservoir. The peripheral adhesive layer 30 is the means by which the device is attached to the skin. The release liner 31 is a conventional removable layer. Accordingly, except for the conductive overlay, device 25 is of conventional reservoir-type structure and design.

In operation, the release liner is removed from the underside of the device and the device is placed on the skin. A heat source is then placed in contact with the conductive layer, and the device and underlying skin are heated as in the case of device 10 of Figure 1.

Although not shown in the depicted embodiments, the devices of the invention may be equipped with a temperature sensor (e.g., a thermocouple or thermistor) located at the interface between the device and the skin, and means coupling the sensor to the heat source by which the heat source may be regulated as needed to maintain the temperature at said interface at a desired level or range.

The following example further illustrates the invention. This example is not intended to limit the invention in any manner.

Example

An acrylate adhesive mixture of 1 part Gelva 737 to 4 parts Gelva 788 by solid weight was prepared. An adhesive solution containing 4% dexmedetomidine, 5% propylene glycol monolaurate and 91% of the adhesive (% w/w of solids, discounting adhesive solvent) was then prepared). This solution was cast using a 2-mil fixed-gap gardner knife onto a 92EB11 Mylar film (DuPont). Cast films were dried in the oven for 30 minutes at 70°C to remove the solvent. A siliconized polyester release liner (H.P. Smith) was then laminated to the adhesive film. Patches were die cut out of the laminate for testing.

Modified Franz vertical cells were used for in vitro penetration studies which were carried out to determine the burst effect. The release liner was peeled off the system prior to placing the system on heat-separated human epidermis. The epidermis and patch were then mounted between the donor and receiver compartments and clamped in place. The receiver compartments were filled with phosphate buffer, pH 5, and the temperature was maintained at 44°C for the first 2 hours and at 32°C thereafter. Samples were taken at preset intervals and assayed by HPLC. The results of these tests are shown in Figure 4.

As shown, the heating markedly enhanced the flux of the dexmedetomidine through the skin.

Modifications of the above-described modes for carrying out the invention that are obvious to those of skill in the chemical, transdermal drug delivery, pharmaceutical and related arts are intended to be within the scope of the following claims.

Claims

1. A method for administering a thermally stable drug transdermally to a human patient via diffusion of the drug from a transdermal drug delivery device affixed to an area of skin of the patient in which the flux of drug through said area is enhanced thermally for a predetermined time period comprising:

(a) applying the device to said area, said device comprising a reservoir of the drug in diffusional communication with said area and having no solid component that melts below 45°C and wherein the drug is thermally stable below 45°C; and

(b) heating the device and said area of skin for said predetermined time period to a temperature substantially above the normal temperature of the skin with the proviso that said area is not heated above 45°C, whereby the flux of the drug through said area is increased.

2. The method of claim 1 wherein said heating occurs promptly after the device is applied to the skin.

3. The method of claim 1 wherein the predetermined time period is in the range of 0.5 to 8 hrs.

4. The method of claim 1 wherein said heating is effected by applying an external source of heat to the device.

5. The method of claim 1 wherein said heating is effected by an exothermal reaction within the device.

6. The method of claim 1 wherein the drug is dexmedetomidine.

7. A device for administering a thermally stable drug transdermally through an area of unbroken human skin comprising in combination:

(a) a reservoir of the drug in diffusional communication with the area of skin, said drug being capable of permeating through said area of skin at normal skin temperature at a first flux and being thermally stable at temperatures below 45°C, said device having no solid component that melts below 45°C; and

(b) means for heating the device and said area of skin to a temperature substantially above normal skin temperature, with the proviso that said area of skin is not heated above 45°C, whereby the flux of the drug through said area of skin when the device and skin are so heated is substantially greater than said first flux.

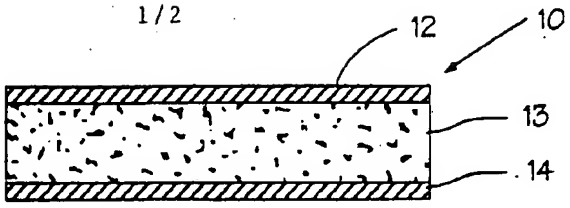


Figure 1

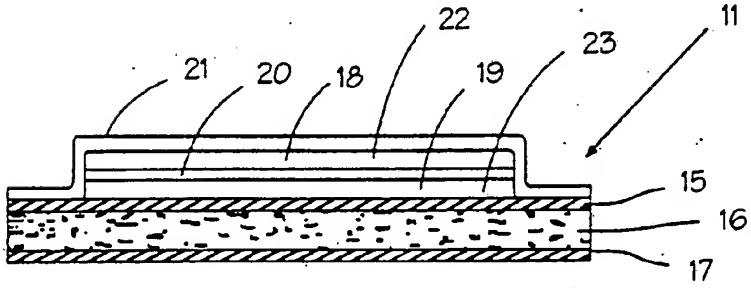


Figure 2

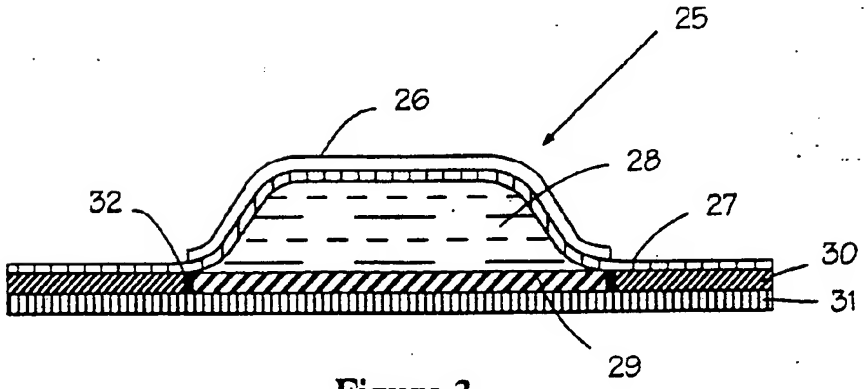
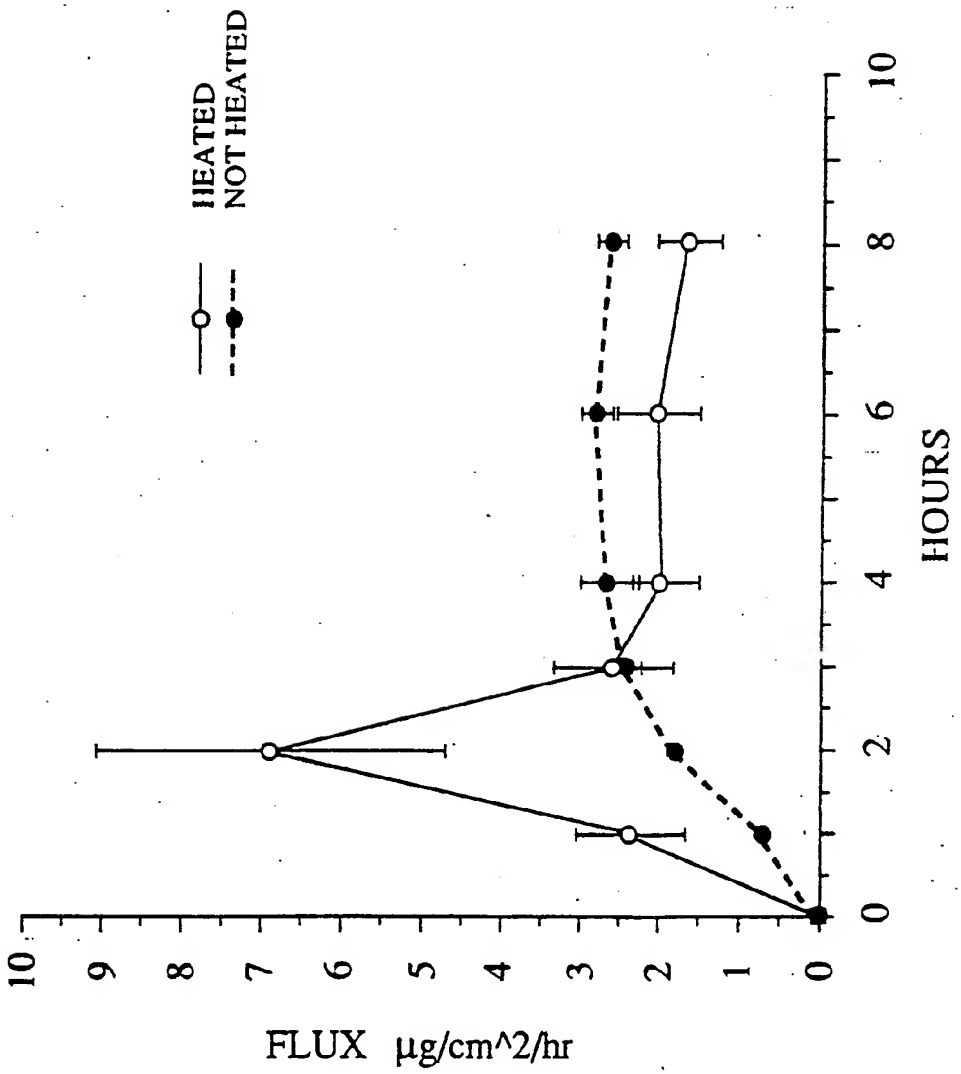


Figure 3

Figure 4


HEATED
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INTERNATIONAL SEARCH REPORT

PCT/US92/08519

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61F 13/00
US CL :424/449
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449, 448, 447

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,879,119 (KONNO ET AL) 07 NOVEMBER 1989; See entire document	1-7
Y,P	US, A, 5,124,157 (COLLEY ET AL) 23 JUNE 1992 See claim 6	6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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